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DOI
10.1016/j.physbeh.2021.113324
Publication date
2021
Document Version
Final published version
Published in
Physiology & behavior

Physiology & Behavior 232 (2021) 113324

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

# Age, BMI, and inflammation: Associations with emotion recognition

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ARTICLE INFO

*Keywords:*
Inflammation
Aging
Body mass index
Reading the mind in the eyes
Emotion recognition
Psychoneuroimmunology

ABSTRACT

Experimental studies show that inflammation impairs the ability to interpret the mental state of another person, denoted theory of mind (ToM). The current study attempted a conceptual replication in states associated with elevated low-grade inflammation, i.e., high body weight and advanced age.

Ninety young ($M = 26.3$ years, $SD = 4.1$) or older ($M = 70.7$ years, $SD = 4.0$) participants with either a normal body mass index (BMI) ($M = 22.4$, $SD = 2.2$) or high BMI ($M = 33.1$, $SD = 3.8$) completed the Reading the Mind in the Eyes Test (RMET) to assess emotion recognition. Plasma interleukin-6 (IL-6) level was measured to index low-grade inflammation.

As anticipated, elevated IL-6 levels were found with higher BMI, although not with increased age. IL-6 was associated with poorer task performance, independent of potential demographic and health confounders (e.g., sex, education, smoking status, alcohol intake, presence of medical conditions, and medication intake). Analyses also revealed an interaction whereby young individuals with a high BMI showed worse RMET performance compared to their normal BMI counterparts, whereas the opposite pattern was found in older individuals.

The present observational study replicated experimental results showing that elevated low-grade inflammation is correlated with a lower ability to infer the mental states of others. These findings suggest that also naturalistic conditions of (protracted) low-grade inflammation may alter emotion recognition.

## 1. Introduction

Human and animal studies have identified acute inflammation as a powerful regulator of social behaviors [1]–[3]. Two recent studies showed that induced acute inflammation impaired the ability to recognize emotions expressed by others, a central component of social cognition [2, 3]. Impairment of emotion recognition is a transdiagnostic mechanism implicated in a number of mental health disorders, most notably depression [4, 5]. For example, impaired emotion recognition is thought to explain why depressed individuals tend to express more social difficulties and exhibit social withdrawal [4, 6]. Whether such inflammatory effects on emotion recognition are also observed in non-experimental, naturalistic conditions characterized by low-grade inflammation remains unanswered.

Protracted low-grade inflammation is seen among individuals with high BMI and in advanced age [7, 8]. In the former, inflammation is thought to emanate mainly from adipose cells and surrounding immune cells that produce copious amounts of inflammatory cytokines [9]. In aging, the sources of elevated inflammatory activity, denoted as "inflammaging", are more diffuse and may involve factors such as oxidative stress, immunosenescence (i.e., age-related immune impairment), hormonal changes, and the gradual surge of inflammatory conditions such as atherosclerosis [10–12]. Age and BMI are therefore relatively independent determinants of low-grade inflammation. Considering that these states are rather stable (i.e., do not change from one week to the other), these factors may be utilized to study the relationship between emotion recognition and persistent low-grade inflammation.

High BMI and older age are associated with lower performance across multiple cognitive domains [13–18]. However, only a handful of studies have addressed the combined effects of BMI and age on cognitive functions, and, to the best of our knowledge, none assessed emotion recognition. These isolated studies show both additive and synergistic effects, whereby obesity-related cognitive deficits are independent of age [19–21] or appear amplified with increased age [22]. Some reports also indicate a possible protective effect whereby the impairments

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https://doi.org/10.1016/j.physbeh.2021.113324
Received 4 September 2020; Received in revised form 8 January 2021; Accepted 18 January 2021
Available online 20 January 2021

associated with high BMI disappear or reverse with increasing age; a phenomenon referred to as the "obesity paradox". For example, older adults with a relatively higher BMI exhibited less decline in selective cognitive domains [23–26]. In a similar vein, poorer memory recall performance over 12 years was predicted by a decline in BMI during that period [27], and low BMI and weight loss in older age precede the onset of dementia [28–30]. Together these data suggest that in older age a lower BMI, rather than higher BMI, may be a risk factor for cognitive decline. However, age-dependent BMI relationships with social cognition, and more specifically emotion recognition, have remained unexplored.

It is expected that both aging and obesity are linked to alterations in emotion recognition, although this may not apply to all emotions equally. E.g., recognition of disgust seems to be preserved with age, whereas the emotions anger and sadness are particularly affected [31, 32]. A meta-analysis of emotion processing studies demonstrated that individuals with obesity have lower levels of emotional awareness and difficulty in using emotion regulation strategies [33]. The evidence for an impaired ability to recognize emotions appeared inconsistent [33]. However, this meta-analysis included only two studies that assessed emotion recognition. Of these two studies, one study reported no differences recognizing the facial expression of others comparing women with women with obesity and women with normal-weight [34], while the other study reported impairments in inferring emotional states in self and others among women with obesity [35]. Moreover, these inconclusive findings were based on studies with young to middle-aged individuals.

Therefore, the aim of the present cross-sectional study was twofold. First, to assess the association of BMI- and age-related low-grade inflammation (as measured by IL-6) with emotion recognition. Second, to determine if age and BMI show independent or interactive associations with emotion recognition.

## 2. Method

### 2.1. Participants

Ninety participants (60% female) were recruited through a database held by the University of Birmingham and via (online) advertisement. Inclusion criteria included an age between 21 and 35 years ('young'; $M = 26.3$, SD = 4.1) or between 63 and 80 years ('older'; $M = 70.7$, SD = 4.0) and a BMI between 17 and 25 ('normal BMI'; $M = 22.4$, $SD = 2.2$) or greater than 27 ('high BMI'; $M = 33.1$, $SD = 3.8$). Height and body weight were confirmed in the laboratory. One participant had a BMI of 26.3 and thus failed to meet the BMI criterion for either the normal BMI or the high BMI group and was therefore removed from all analyses. Individuals who reported a history of gastric banding, eating disorders, neurological or inflammatory disorders (e.g., rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, periodontitis) or use of anti-depressant, anti-histamine, or anti-inflammatory (e.g., antibiotics) medication during the past 7 days were excluded before participation. Participants reported normal or corrected-to-normal vision and stable body weight for at least six months (i.e., fluctuations $< 7.5$ kg for individuals with high BMI, $< 5$ kg for normal BMI individuals). The participants were paid a maximum of £25 to reimburse travel expenses. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the University of Birmingham Research Ethics Committee.

### 2.2. Procedures

Test sessions started throughout the day between 8:30 and 15:30 h. Start times of test sessions were matched across the four groups to control for diurnal variations in IL-6 [36]. Written informed consent was obtained on arrival. Participants were instructed to have their breakfast/lunch as usual but to avoid consumption of high-fat products (e.g., bacon, fries), because these foods may induce a short-lived inflammatory response [37], and to refrain from eating, drinking (except for water), and smoking for 1 hour before the start of the test session. Participants were also asked not to engage in strenuous physical exercise or consume alcohol within 12 h before the test session, and reschedule their appointment if they had a suspected infection or infection symptoms on the day of testing. Self-reports were used to verify whether participants had complied with instructions. A blood sample was taken by venipuncture and questionnaires and cognitive tests were completed, including the reading the mind in the eyes test (see further below). Other tests included measures of attention and psychomotor speed (published elsewhere [21]), memory, and learning. The order in which the tasks were administered was fixed and the same across all the participants. Lastly, a measure of height and body composition was taken.

## 3. Materials

### 3.1. Reading the mind in the eyes test

The reading the mind in the eyes test (RMET) is considered an advanced test of theory of mind involving mental state attribution and complex emotion recognition from photographs of the eye region of the face [38, 39].

#### 3.1.1. Procedure

The test display comprised a test eye image and four words placed in the center of the screen. The participant was instructed to select the word that best described what the person in the test image was thinking or feeling by pressing one of four computer keys (Q, P, A, L) that spatially corresponded to the position of each word. The correct (target) word had the same emotional valence as the accompanying three foil words. For example, the target word, 'panicked', was accompanied by 'arrogant', 'jealous' and 'hateful'. Target words were equally likely to appear in one of the four word locations on the screen. Each test display remained visible until a key response was made; the next test display was immediately presented thereafter. The test consisted of 36 different test images, completed as one set. In line with previous studies, a glossary containing a definition of each word was available to the participant.

#### 3.1.2. Stimuli

A gray-scale digital image (subtending 9 x° X 3.6 y° of visual angle) of the eye region of a face (including eyes and eyebrows) was presented in the middle of a gray field on a computer monitor. Four words describing mental states accompanied each test stimulus, presented in black Arial font (subtending 2.6 x° X 0.7 x° of visual angle).

### 3.2. Blood sampling

Blood (6 mL) was collected from an antecubital vein in the forearm into one vacutainer containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant (Becton Dickinson Diagnostics, Oxford, United Kingdom). Samples were immediately centrifuged at 1500 g for 10 min at 4 °C and plasma was aliquoted and stored at −80 °C for later assessment of interleukin-6 (IL-6), a marker of systemic low-grade inflammation. Plasma level of IL-6 was measured in duplicate using high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine HS Human IL-6 ELISA, R&D Systems, UK) in accordance with the manufacturer's instructions. The limits of detection of this assay was 0.11 pg/mL, with intra- and inter-assay coefficients of variation (CVs) of 0.69–11.6%.

### 3.3. Anthropomorphic measures

Participants were asked to remove footwear and coats and empty their pockets before a body composition measurement was taken using a

TANITA BC-545N body composition analyzer (Tanita Europe, Amsterdam, The Netherlands). A stadiometer was used to measure height.

### 3.4. Questionnaires

To adjust for potential confounding factors, participants completed questionnaires about presence of common medical conditions (modified version of self-administered comorbidity questionnaire (SCQ), allowing to mention an unlimited number of 'other medical problems, please enter' ; [40]), sleep quality (Pittsburgh Sleep Quality Index (PSQI); [41]), medication intake (number of medications), and demographic variables (i.e., age, sex, occupation status, education, smoking status (current smoker, ex-smoker, non-smoker), alcohol intake (units per week)).

## 4. Statistical Analyses

Data from participants who disproportionally biased mean estimates were removed using Cook's Distance and data points that exceeded 3 *SDs* from means ($n = 2$, young high BMI individuals with an average accuracy < 30%).

For IL-6 analysis, log transformation was applied because of the skewed distribution of raw IL-6 values. There were six missing values (five young high BMI and one older high BMI participant). Outliers (values > 3 *SDs* from group means) were removed ($n = 3$, 2 = older normal BMI, 1 = young high BMI). The IL-6 results are also published elsewhere [21] with slight deviations due to missing data and test-specific exclusion criteria.

To assess a relationship between low-grade inflammation and RMET performance, initial correlation analysis was performed. Multiple linear regression analysis was conducted to assess whether a significant correlation between low-grade inflammation and RMET performance was independent of age, BMI, time of day, demographic-, lifestyle- and health-factors, using: 1) an unadjusted model with IL-6, and 2) an adjusted model correcting for age, BMI, demographic-, lifestyle- and health-variables (i.e., medical conditions , smoking, alcohol intake, sleep quality, medication intake, sex, education level) previously shown to be associated with inflammation and/or cognitive function. The results of the multiple regression models are presented as standardized coefficient estimates ($\beta$), *t*-values, and 95% confidence intervals. In the event of a significant relationship between inflammation and overall RMET performance, mediation analysis was conducted.

To assess possible additive and/or interactive correlational, not causal associations of age and BMI with RMET performance, the percentage of total correct responses was calculated and Age group (young, older) and BMI group (normal BMI, high BMI) were entered as between-subject factors in an analysis of variance (ANOVA). To assess the effect of emotional valence, percentage correct was calculated for each emotional valence (positive, neutral, and negative expressions) [42], which was entered in a mixed model ANOVA. Previous studies reported sex differences in emotion recognition [43–46] but because the study was not designed to assess sex-dependent effects, sex was included as a covariate rather than a between-subjects factor (see Supplementary Materials for exploratory analysis including sex as a between-subjects factor).

Alpha values were set at 0.05 throughout. For all analyses where appropriate, Levene's test of Equality of Variances and Mauchly's Test of Sphericity were used to test for assumption violations; adjustments were made as needed using the Greenhouse-Geisser correction. Bonferroni corrections were applied to post-hoc pairwise comparisons (two-tailed unless stated otherwise) to control for Type I error rate. The PROCESS macro [47] was used to test possible mediation effects of IL-6 (Model 4 with 5000 bootstrap samples). In addition to traditional null hypothesis significance testing, Bayes factors were calculated using Bayesian ANOVAs, t-tests, and correlational analyses using default prior probabilities (see [48] for guidelines on the interpretation of Bayes factor). All statistical analyses were conducted using SPSS v.24.0 (IBM-SPSS Inc., Chicago, IL, USA) and JASP version 0.13.

## 5. Results

### 5.1. BMI, age, and inflammation

Table 1 presents summary statistics of the included participants ($n = 87$). The four groups did not differ in sex composition, age (i.e., between the BMI groups), or BMI (i.e., between the age groups). The IL-6 analysis and an extended table of descriptive statistics are also published elsewhere [21]. ANOVAs showed higher IL-6 levels in the high versus normal BMI group ($F(1, 78) = 31.30$, $p < .001$, $\eta_p^2 = 0.29$, $BF_{10} = 39$, 511.14), and higher IL-6 levels in the older versus young group ($F(1, 78) = 3.62$, $p = .061$, $\eta_p^2 = 0.04$, $BF_{10} = 1.10$) although the latter was non-significant. There was no evidence for an age x BMI group interaction ($F(1, 76) = 2.38$, $p = .127$, $\eta_p^2 = 0.03$; $BF_{10} = 1.33$).

### 5.2. Inflammation and emotion recognition

As can be seen in Fig. 1, mean performance on the RMET (averaged across valence) was significantly negatively correlated with IL-6 ($r(80) = -0.279$, $p = .012$, $BF_{10} = 3.06$). Multiple regression analysis confirmed that IL-6 remained a significant predictor of mean RMET performance when adjusting for age and BMI group, time of day, and demographic-, lifestyle- and health-variables (adjusted model) (see Table 2).

Repeating the regression analysis with age and BMI as a continuous factor produced similar results (see Supplementary Materials Table S1). Inflammation had no mediating role in the relationship between inflammation and emotion recognition (results reported in Supplementary Materials).

### 5.3. Age-dependent bmi effects on emotion recognition

As can be seen in Fig. 2a, an age x BMI group interaction ($F(1, 82) = 12.01$, $p < .001$, $\eta_p^2 = 0.13$, $BF_{10} = 45.61$) showed that young individuals with a high BMI ($M = 62.7\%$, $SE = 2.6\%$) performed worse than their normal BMI counterparts ($M = 73.3\%$, $SE = 2.6\%$) (controlling for sex) ($t(38) = 2.74$, $p = .010$, $d = 0.85$, $BF_{10} = 5.27$). In contrast, in the older group, a main effect of BMI group indicated that individuals with a high BMI ($M = 73.1\%$, $SE = 2.3\%$) outperformed those with a normal BMI ($M = 66.1\%$, $SE = 2.6\%$) (controlling for sex) ($t(45) = -2.07$, $p = .044$, $d = -0.60$, $BF_{10} = 1.65$). Moreover, additionally adjusting for health symptoms and time of day (age x BMI interaction: produced similar results $F(1, 820) = 9.26$, $p = .003$, $\eta_p^2 = 0.10$). Using age- and sex-

**Table 1**
Descriptive statistics of participant characteristics. Numbers in parenthesis indicate SD; ◆ indicates a significant main effect of age group, • indicates a significant main effect of BMI group.

| | Young Normal BMI | Young High BMI | Older Normal BMI | Older High BMI |
|---|---|---|---|---|
| N | 20 | 20 | 21 | 26 |
| Age (years) | | | | |
| Mean◆ | 25 | 28 | 72 | 70 |
| Range | 21 – 32 | 21 – 35 | 66 – 79 | 63 – 76 |
| Sex (*n* Female) | 11 | 14 | 13 | 15 |
| IL-6 (pg/ml)• | 1.04 ± 0.44 | 2.40 ± 1.24 | 1.67 ± 1.36 | 2.35 ± 1.03 |
| Range | 0.34 –2.10 | 1.12 – 5.61 | 0.43 – 6.54 | 1.09 – 5.99 |
| Weight Status | | | | |
| BMI ($kg/m^2$)• | 21.7 ± 2.5 | 33.1 ± 3.4 | 23.0 ± 1.7 | 32.5 ± 3.8 |
| Body fat% | | | | |
| Females• | 27.9 ± 3.9 | 45.9 ± 4.7 | 33.3 ± 5.6 | 44.9 ± 4.8 |
| Males• | 15.7 ± 4.4 | 27.6 ± 3.8 | 22.4 ± 5.0 | 31.8 ± 4.9 |
| Medical conditions score (SCQ)◆ | 0.95 ± 1.3 | 1.3 ± 1.9 | 3.0 ± 2.3 | 5.1 ± 3.2 |

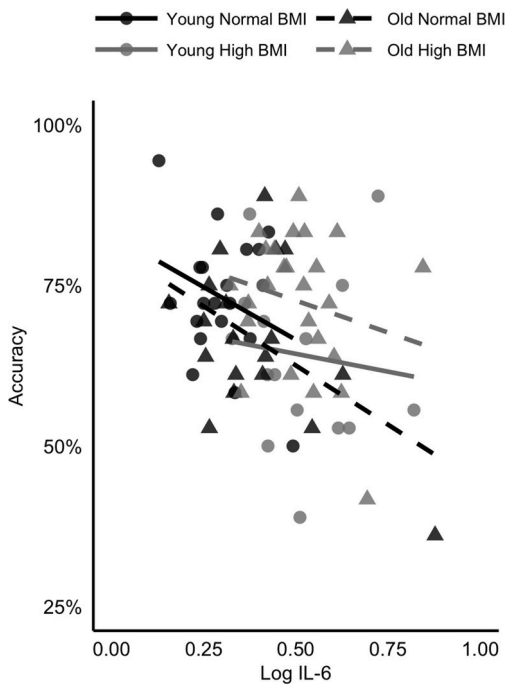


**Fig. 1.** Scatterplot depicting individual accuracy scores and IL-6 levels. For each subgroup linear regression lines are fitted. Please note that the y-axis starts at chance level (i.e., 25% accuracy).

**Table 2**
Multiple regression analysis ($N$ = 80) of the relationship between IL-6 and overall emotion recognition (model 1) adjusted for influences of age, BMI, time of day, and health- and demographic variables (adjusted model). Age group: 1 = young, 2 = older; BMI group: 1 = low BMI, 2 = high BMI; Sex: 1 = Female; 2 = Male; Smoke: 0 = never, 1 = ex-smoker, 2 = smoker; Alcohol intake in units; Medical conditions = higher number indicates more or more severe medical conditions; Sleep quality: higher score is indicative of lower quality of sleep; Medication intake = number of medications; *** $p < .001$, ** $p < .01$, * $p < .05$.

| | Overall emotion recognition Model $R^2 = 0.08$* Adjusted model $R^2 = 0.25$* | | | |
|---|---|---|---|---|
| | $\beta$ | $t$ | 95% CI | |
| | | | Lower | Upper |
| Model 1 | | | | |
| IL-6 | −0.280* | −2.558 | −0.484 | −0.060 |
| Adjusted model | | | | |
| IL-6 | −0.375** | −2.902 | −0.616 | −0.114 |
| Age group | 0.007 | 0.049 | −0.258 | 0.271 |
| BMI group | 0.070 | 0.530 | −0.185 | 0.319 |
| Sex | −0.132 | −1.089 | −0.353 | 0.104 |
| Education | 0.087 | 0.715 | −0.159 | 0.337 |
| Smoking | 0.142 | 1.164 | −0.095 | 0.361 |
| Alcohol | −0.102 | −0.787 | −0.334 | 0.145 |
| Medical conditions | 0.435* | 2.304 | 0.060 | 0.834 |
| Sleep quality | 0.045 | 0.383 | −0.189 | 0.279 |
| Medication intake | −0.201 | −1.144 | −0.549 | 0.149 |
| Time of day | −0.034 | −0.308 | −0.239 | 0.175 |

adjusted body fat percentages (see [49]) instead of BMI to define weight-groups did not yield a different pattern of results ($F(1, 82) = 6.46$, $p = .013$, $\eta_p^2 = 0.07$). RMET accuracy of young individuals with a body fat percentage indicative of overweight performed 11.1% worse ($SE$ = 3.8%) as compared to their leaner counterparts. In older individuals, those with overweight body fat percentages performed 2.5% better ($SE$ = 3.8%) as compared to their leaner counterparts.

Stimuli selected on valence (negative, neutral, positive) showed that performance was best on positive expressions ($M$ = 78.2%, $SE$ = 1.9%), followed by neutral ($M$ = 69.4%, $SE$ = 1.6%) and negative expressions ($M$ = 63.5%, $SE$ = 1.9%), with significant differences between all three valence types ($F(2, 166) = 24.92$, $p < .001$, $\eta_p^2 = 0.23$, $BF_{10} = 3.735e+7$). As shown in Fig. 2b, the data provided no evidence for an age or BMI group x valence interaction ($F$'s < 1, $BF_{10}$ = 0.11 and $BF_{10}$ = 0.14, respectively).

## 6. Discussion

The present study examined the relationship between inflammation and emotion recognition. As expected, BMI was linked to elevated inflammatory activity, assessed as plasma IL-6. The expected positive association with age was non-significant. In line with earlier experimental research [2, 3], low-grade inflammation correlated with impaired performance on the RMET. This association withstood full adjustment for demographic-, lifestyle- and health-variables. The direct effects of BMI appeared non-linear however, whereby young individuals with a high BMI performed worse on the RMET than their normal BMI counterparts, whereas the reverse was observed for older adults. Analyses could not confirm a mediating role of IL-6 in these group differences, although this may reflect low statistical power.

The current results are consistent with the hypothesis that low-grade inflammation in a non-experimental setting may be a biobehavioral pathway linked to impaired emotion recognition, and further may be taken to suggest that 'normal' variations in inflammatory activity within relatively healthy populations is associated with impaired emotion recognition. The fact that the prevalence of overweight and obesity has reached epidemic proportions worldwide [50], and the majority of these individuals likely have elevated levels of inflammatory activity, adds relevance to this notion. Being less sensitive to such social cues may have direct consequences for the dynamics of social interactions. The present findings are also consistent with preliminary evidence that high BMI is associated with reduced emotion recognition, which some studies have already established in children and adolescents [51–53] but see also [54].

Evidence of an 'obesity paradox' is mostly limited to studies using global measures of cognition, such as the Mini Mental State Examination Test, and focused on so-called 'cold' cognitions (e.g., memory, attention) [24–26], [55]. The current study is the first to extend these observations to cognitive processes that have social-affective components (i.e., so-called 'hot' cognitions).

At present, it remains unclear how or under what conditions older individuals may be spared for BMI-related cognitive deficits [56]. For that reason, some have attributed this "obesity paradox" to methodological issues. Several methodological limitations may indeed apply to the current analyses also. It has been argued that BMI may not represent a reliable index of adiposity in older individuals, because in aging adipose tissue increase is often without weight gain due to a parallel decrease in lean body mass (e.g., muscle mass) [57]. However, when the current analyses replaced BMI by using age- and sex-adjusted body fat percentages to define weight-groups (see [49]), analyses did not yield a different pattern of results (see Results sections). Related to this are findings that patients with cardiovascular disease who have abdominal obesity in combination with a low BMI, are at higher risk of mortality, suggesting that the fat distribution plays an important role in BMI-health relationships [58, 59]. A second caveat is potential of selection bias; i.e., it cannot be excluded that the older high BMI group recruited in the present study may represent a healthier subsample of high BMI adults than in the general population, because heavier individuals may have experienced more overweight-related diseases that prevented them from taking part in research (i.e., those available for research are a relatively healthy subsample) [60]. However, no stringent health-related exclusion criteria were applied in the current study, and accordingly the older high BMI group indeed reported significantly worse levels of medical

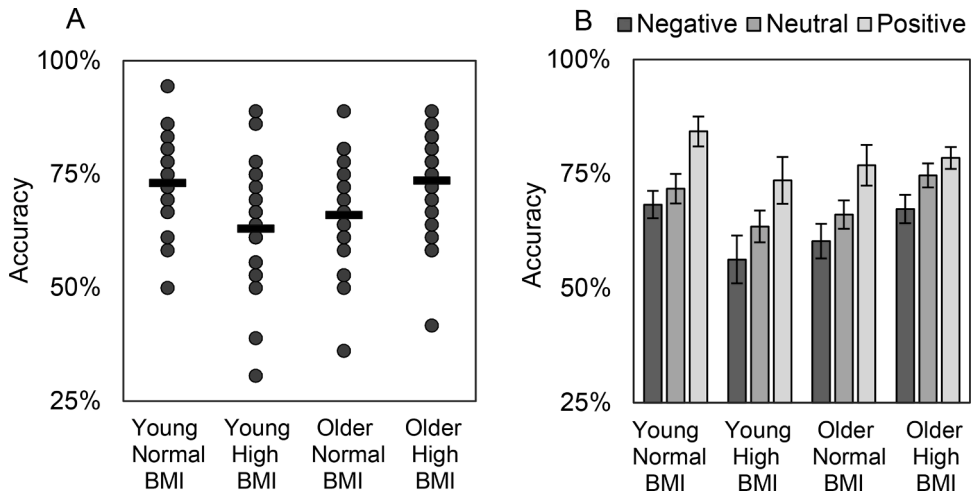


**Fig. 2.** Individual (dots) and group mean (horizontal bars) accuracy scores for RMET total score (A), and group means for each emotional valence for each BMI and Age group (B); Errors bars indicate standard error of the mean. Please note that the y-axes start at 25% accuracy (i.e., chance level).

conditions (see Table 1). Moreover, adjusting for medical conditions did not alter the pattern of results. Thirdly, while there are links between obesity and depression in middle-aged and older adults [61, 62], there are also reports suggesting that depression in older age is associated with weight loss rather than with obesity [63, 64]. These data suggest that a lower BMI in older age may be a risk factor for disturbances in emotional processes. To reduce potential influences of age-related weight loss, stable body weight for at least six months prior to study enrollment was an inclusion criterion in the current study. However, whether weight loss may have occurred before this six month period cannot be ruled out. A further limitation is the moderate sample size and null-findings, including the lack of mediation, should thus be interpreted with some caution. Notwithstanding, to address these potential issues, future research should strive for larger and representative samples. Lastly, the assessment of IL-6 primarily acted as an inflammation check, i.e., a correlate/marker of inflammation, and no causal assumptions about the role of IL-6 in the observed effects can be made. Another inflammatory factor or process mechanistically linked to inflammation may be the causal factor.

In summary, the present observational study aimed to replicate experimental human results and showed that elevated low-grade inflammation was negatively correlated with emotion recognition. In young participants, higher BMI was associated with poorer emotion recognition whereas the opposite was observed for older participants. However, these relationships did not appear to be mediated by IL-6. Protracted low-grade inflammation, in otherwise predominantly healthy individuals, may thus present a biobehavioral pathway influencing emotion recognition across age and body weight categories. A possible protective effect of high-body weight in older individuals warrants further scrutiny.

## Funding and Disclosure

This research was funded by internal funds of the University of Amsterdam and University of Birmingham. The authors report no conflicts of interest, financial or otherwise.

## Acknowledgements

The authors would like to thank Anne Clemens, Greta Ontrup, and Marina Wissink for their valuable contribution in recruiting and testing participants.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2021.113324.

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